



Armed Forces College of Medicine AFCM





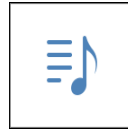
Alternative Fuel to the Heart: Fatty Acid Synthesis

Dr. Naglaa Fathy, MD

INTENDED LEARNING OBJECTIVES (ILOs)



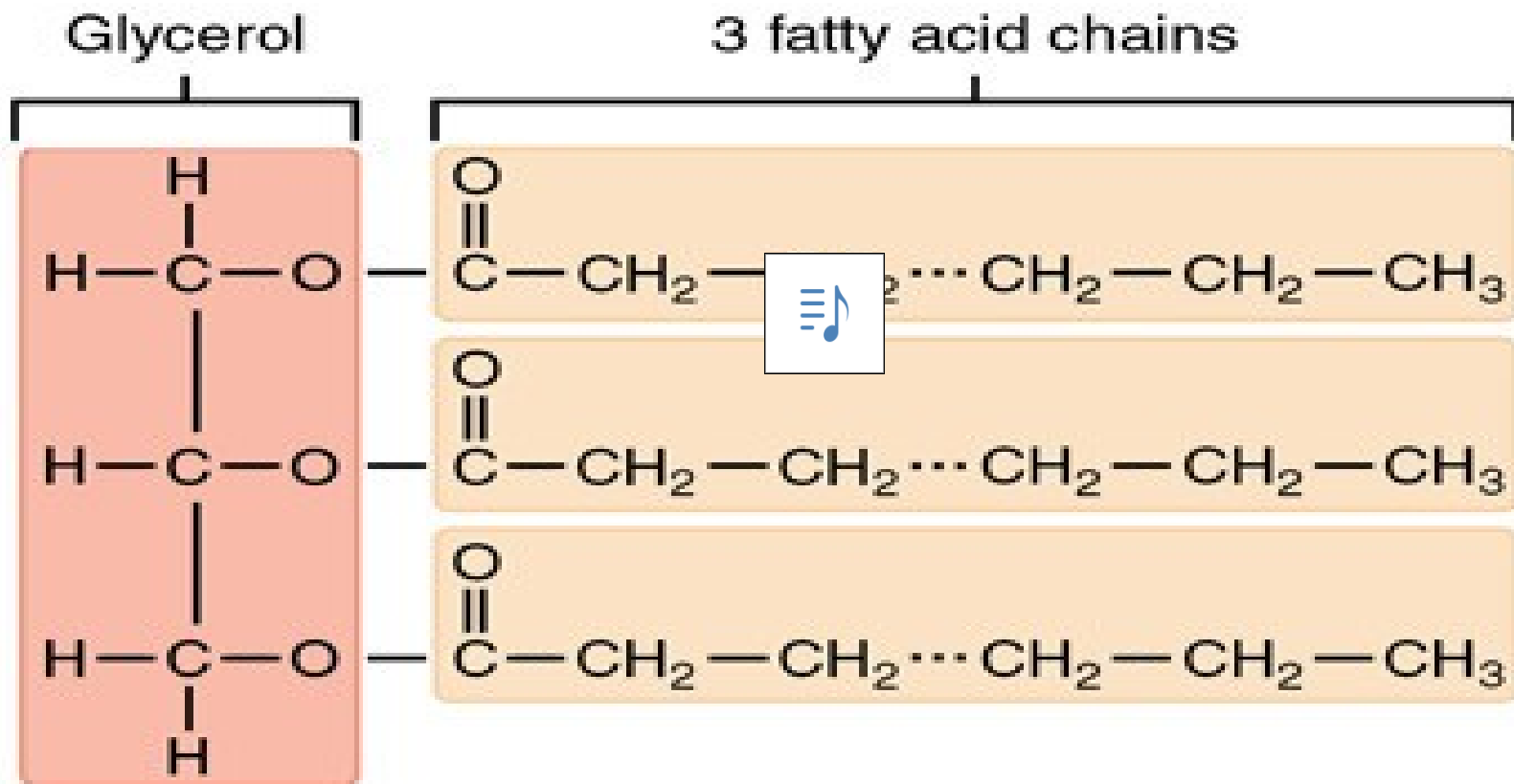
➤ **By the end of this lecture, You will be able to:**



- 1. Illustrate the steps of FA synthesis.**
- 2. Interpret its regulation.**
- 3. Outline important fates of fatty acids.**



Triglyceride



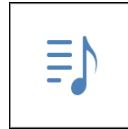
<https://alevelbiology.co.uk/notes/simple-lipids-fats-oils-waxes/>



Synthesis of Fatty Acids

There are two systems for fatty acid synthesis

I- Cytosolic de novo fatty acid synthesis



II- Microsomal system for fatty acid desaturation & elongation



I- Cytosolic De Novo Fatty Acid Synthesis

Acetyl-CoA
(from GLUCOSE)



Palmitic acid
(Mainly)
It is called the **stem**
FA

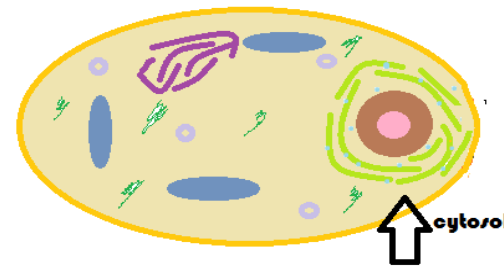


Edited from: <https://www.quora.com/How-is-it-beneficial-to-prefer-complex-carbs-over-simple-carbs>

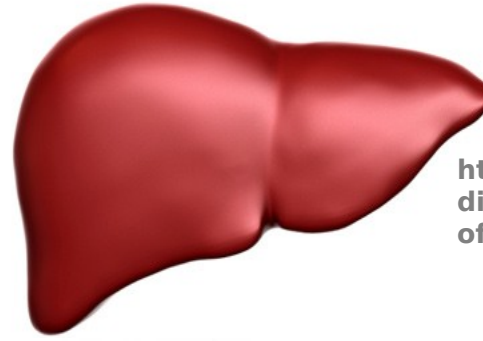
I- Cytosolic De Novo Fatty Acid Synthesis

► **Site:** Occurs primarily in liver, lactating mammary glands

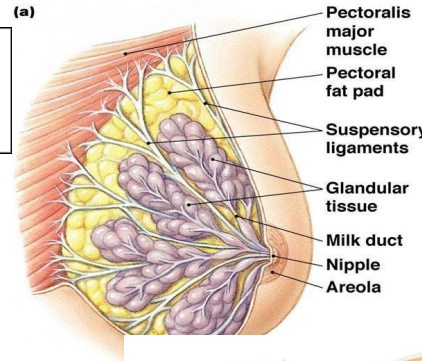
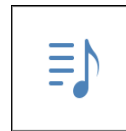
► **To a lesser extent, in adipose tissue**



<https://canyoucellme.weebly.com/cytosol.html>



<https://www.webmd.com/digestive-disorders/picture-of-the-liver#1>

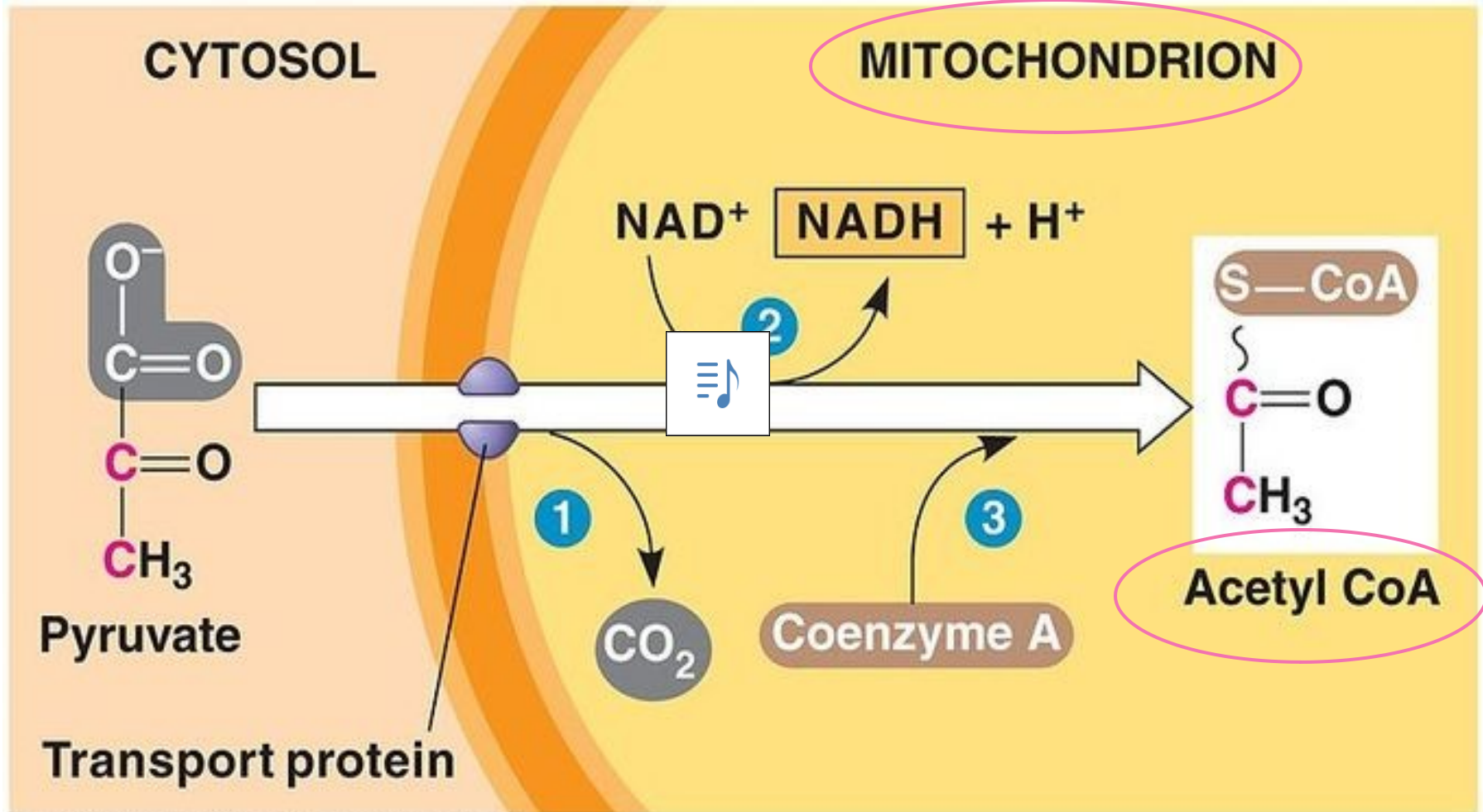


<https://www.quora.com/What-is-the-milk-storage-chamber-in-the-mammary-glands>



https://www.123rf.com/photo_114863529_stock-vector-adipose-tissue-anatomy-vector-realistic-illustration-white-background.html

I- Cytosolic De Novo Fatty Acid Synthesis



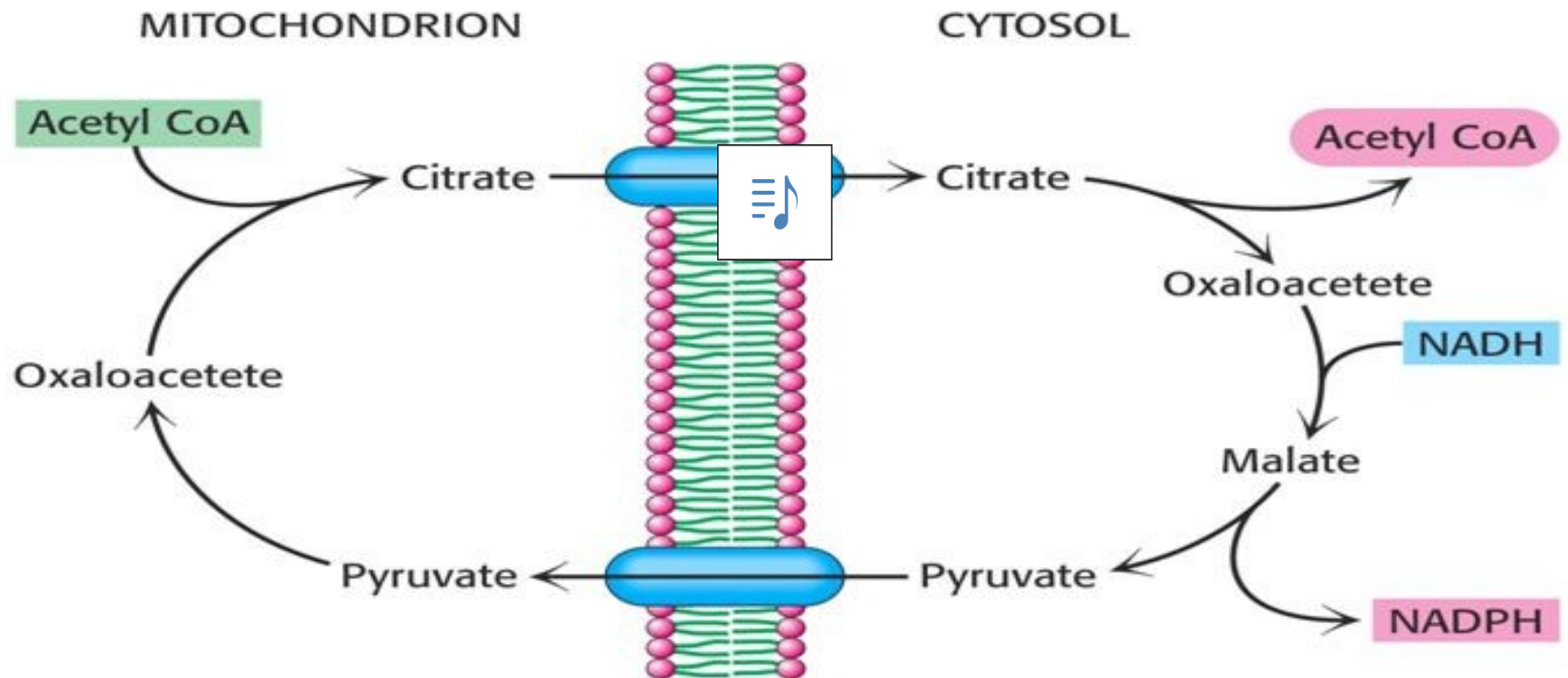
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https://en.wikibooks.org/wiki/Structural_Biochemistry/Pyruvate_Dehydrogenase_Complex

I- Cytosolic De Novo Fatty Acid Synthesis

► Citrate Shuttle

(For transport of Acetyl CoA from mitochondria to cytoplasm)

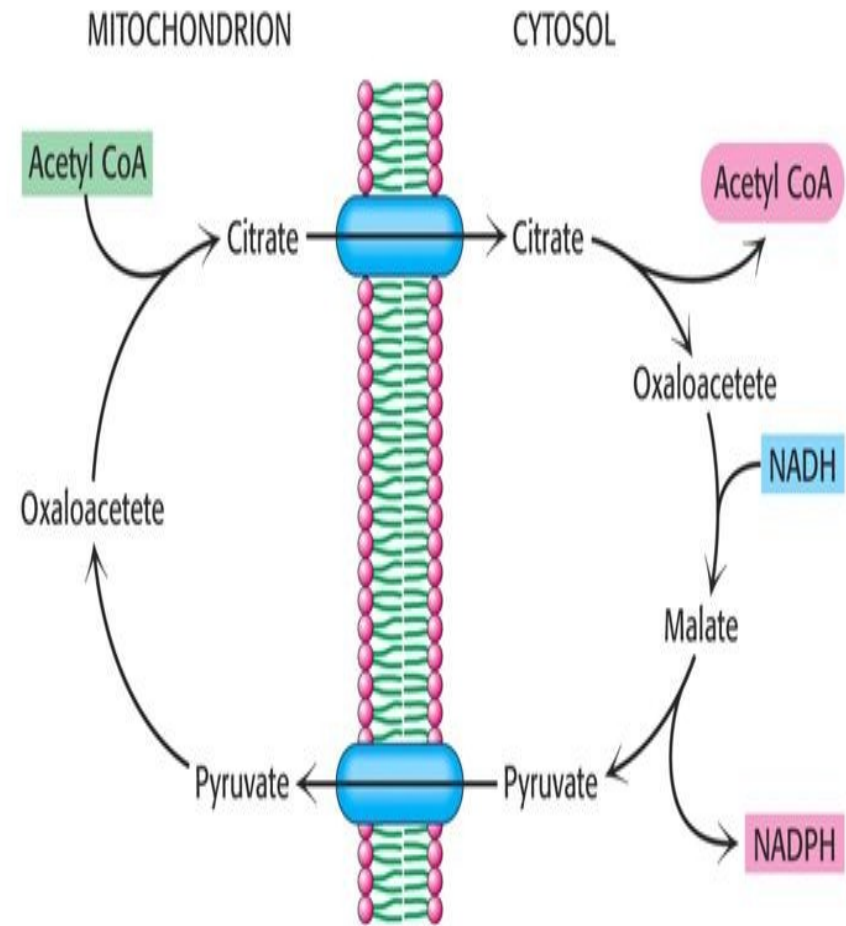


https://www.chem.uwec.edu/chem454_s03/pages/Overheads/C454_lect9_print.pdf

I- Cytosolic De Novo Fatty Acid Synthesis

► Citrate Shuttle:

1. Importance
2. Citrate synthase
3. ATP citrate lyase.
4. Oxaloacetate returns to the mitochondria (as pyruvate or malate) to translocate more acetyl-CoA.



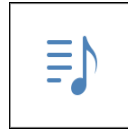
https://www.chem.uwec.edu/chem454_s03/pages/Overheads/C454_lect9_print.pdf

For fatty acid synthesis, acetyl CoA should be transported into the cytosol. How could this be solved?

a) Carnitine shuttle

b) Citrate shuttle

c) Malate shuttle



d) Glycerol 3 Phosphate shuttle

e) BPG shuttle



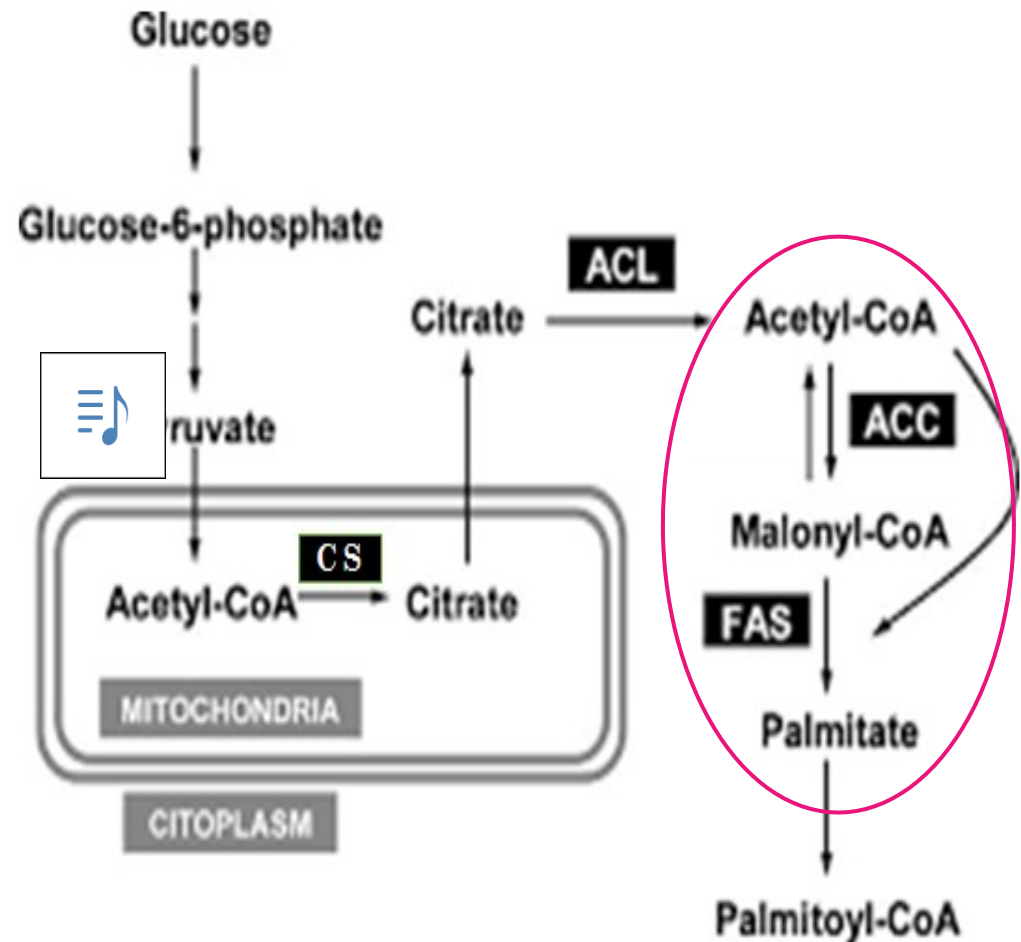
Steps of fatty acid synthesis

1. **Acetyl CoA carboxylase (ACC).**

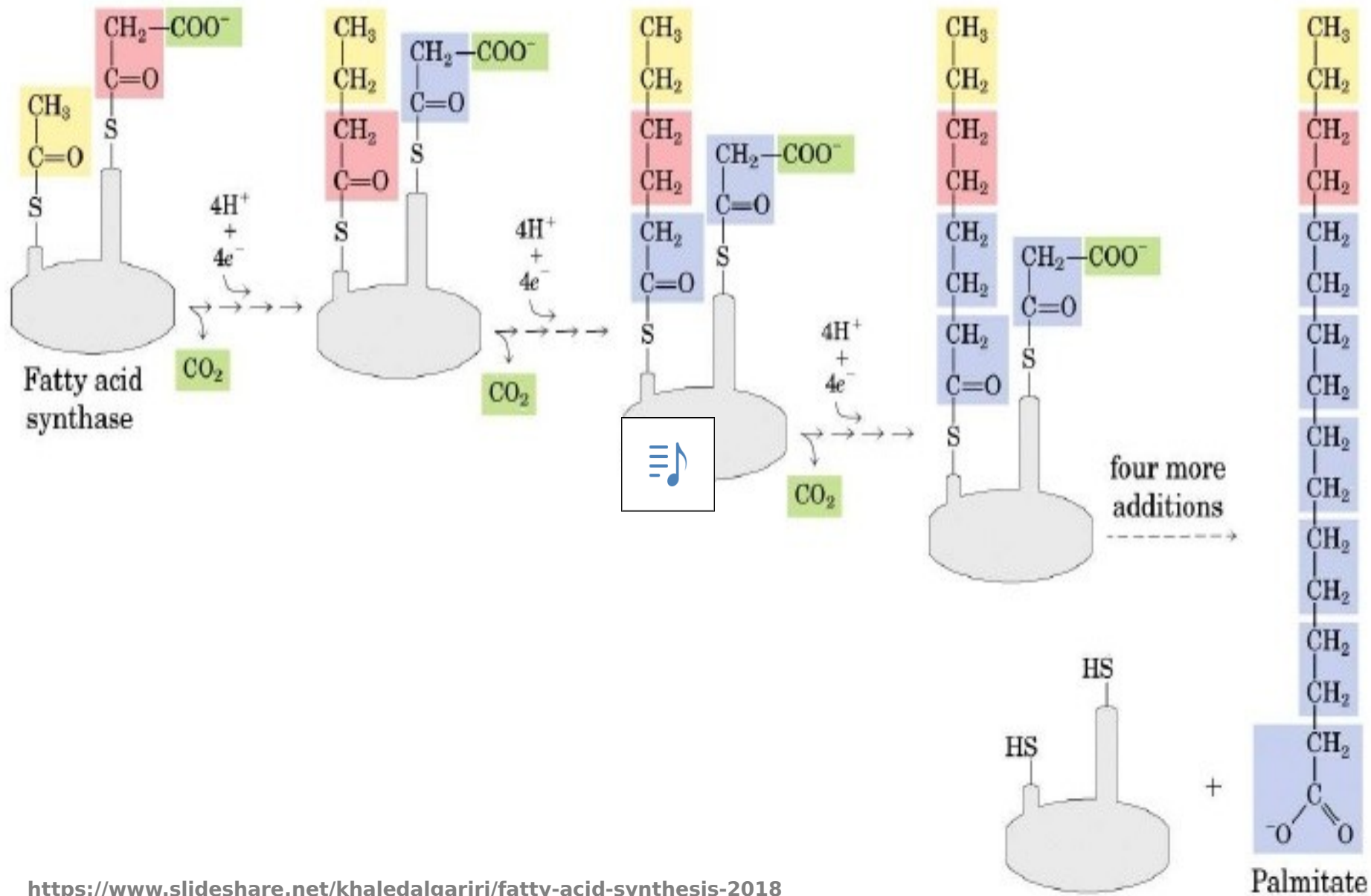
2. **Fatty acid synthase (FAS)**

(Acting in consequence)

CS: Citrate Synthase, **ACL**: ATP Citrate Lyase, **ACC**: Acetyl CoA Carboxylase, **FAS**: Fatty acid synthase,



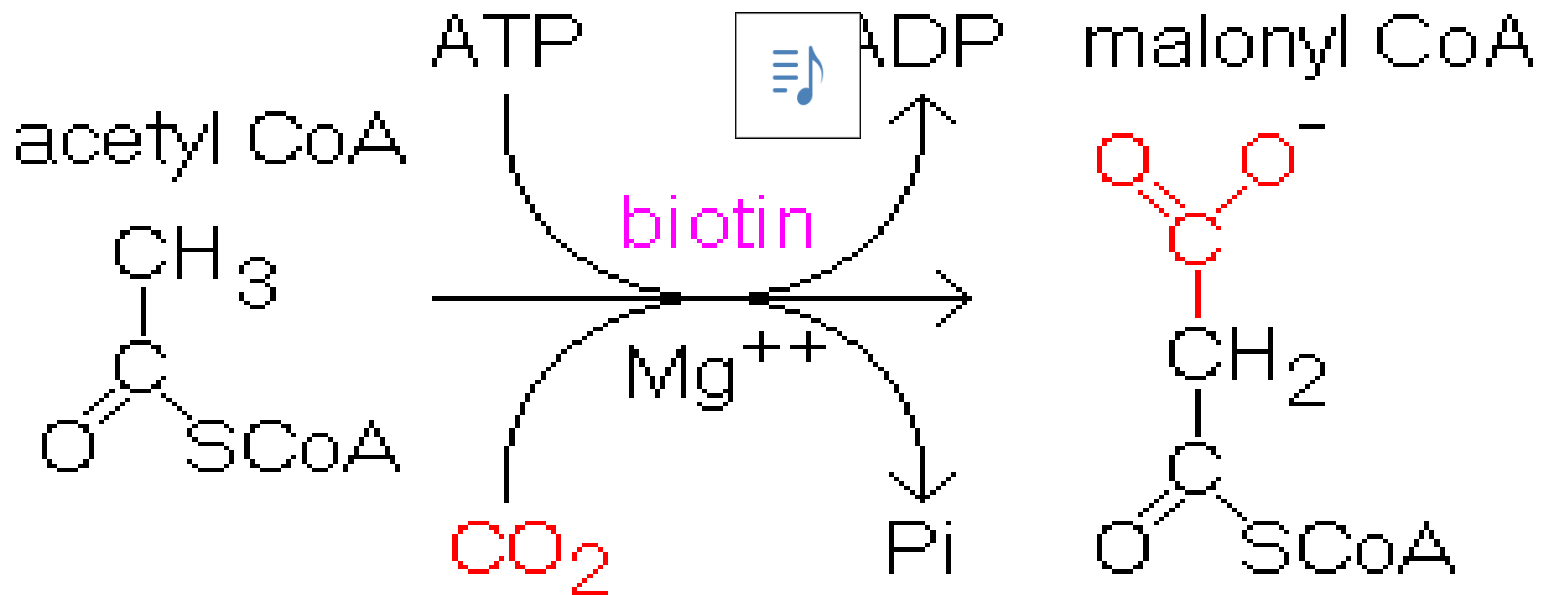
Edited from: <http://diabetes.klebos.net/documents/fat.pdf>



Steps of fatty acid synthesis

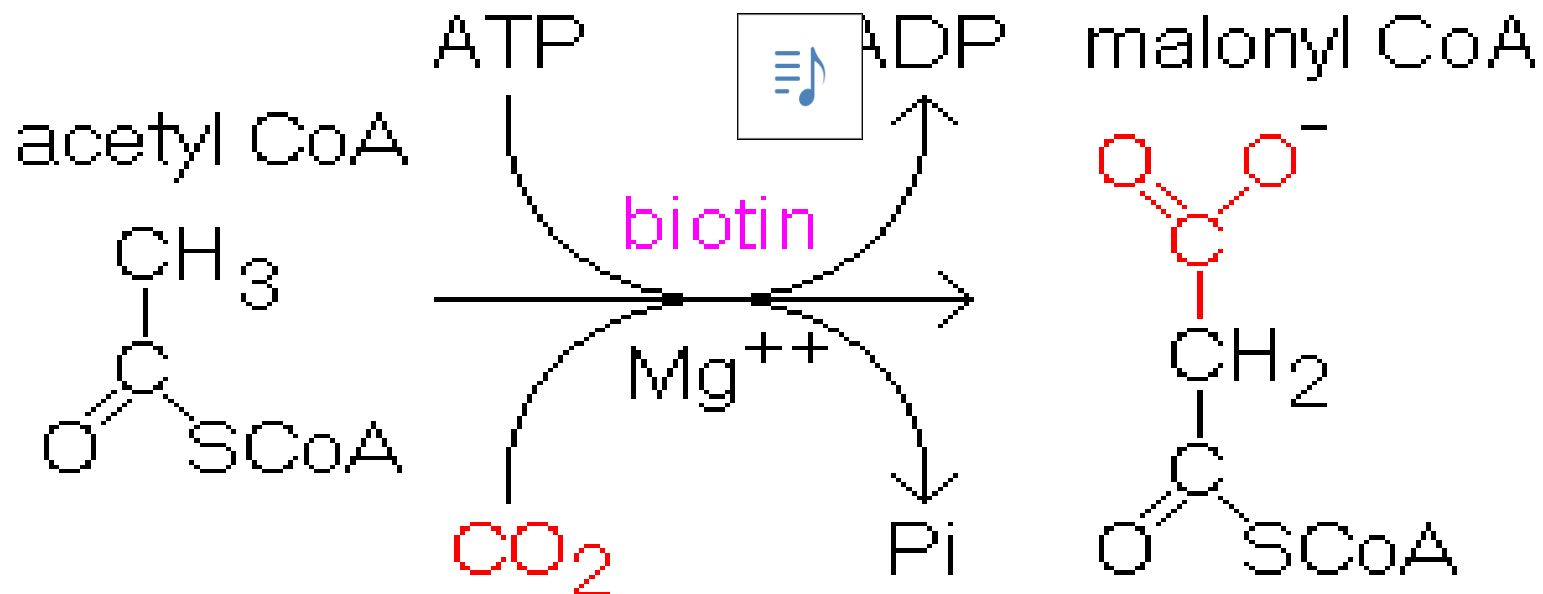
1. Acetyl CoA carboxylase (ACC):

It is used to form malonyl-CoA which is the source of the two carbons that are used to elongate the FA.



<http://www.bmb.leeds.ac.uk/illingworth/medics1/liver.htm>

The First Step is Carboxylation of Acetyl CoA to Malonyl CoA by Acetyl CoA Carboxylase (**ACC**)
(The committed/ The rate limiting step)



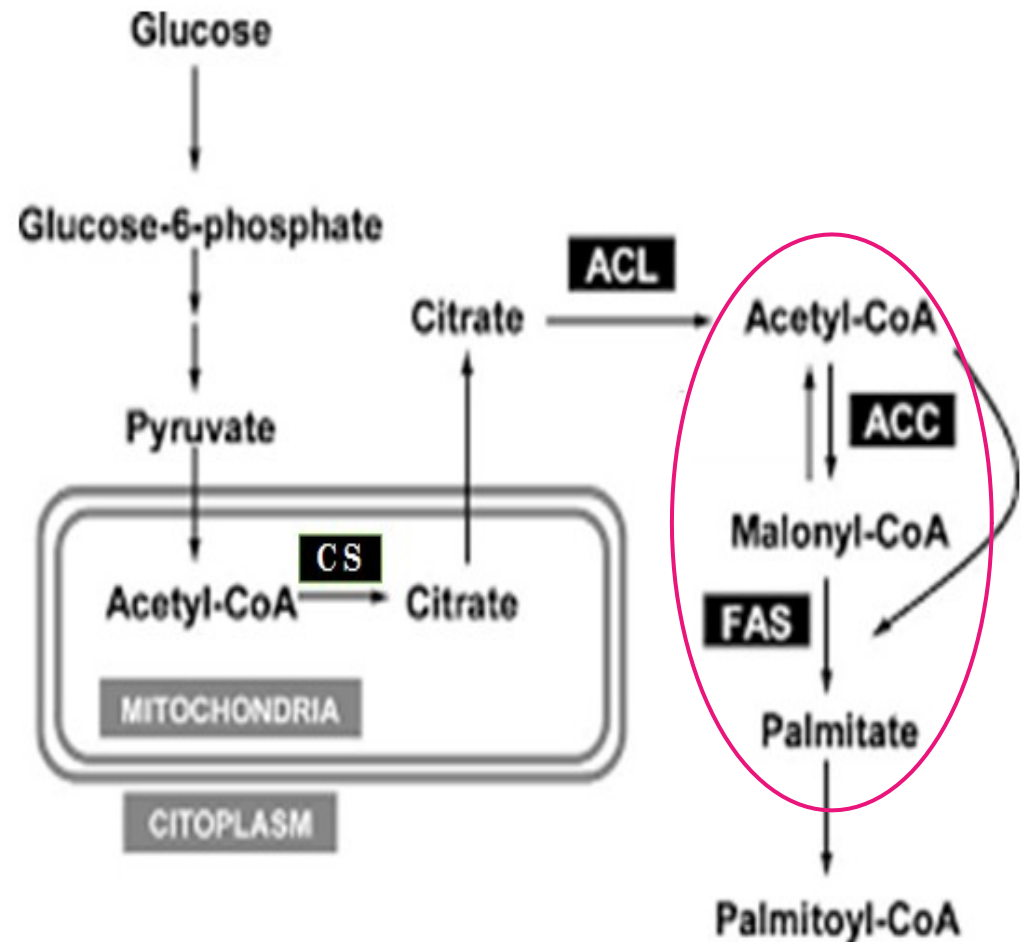
<http://www.bmb.leeds.ac.uk/illingworth/medics1/liver.htm>

Remember!!

Steps of fatty acid synthesis

1. **Acetyl CoA carboxylase (ACC).**
2. **Fatty acid synthase (FAS)**

(Acting in consequence)

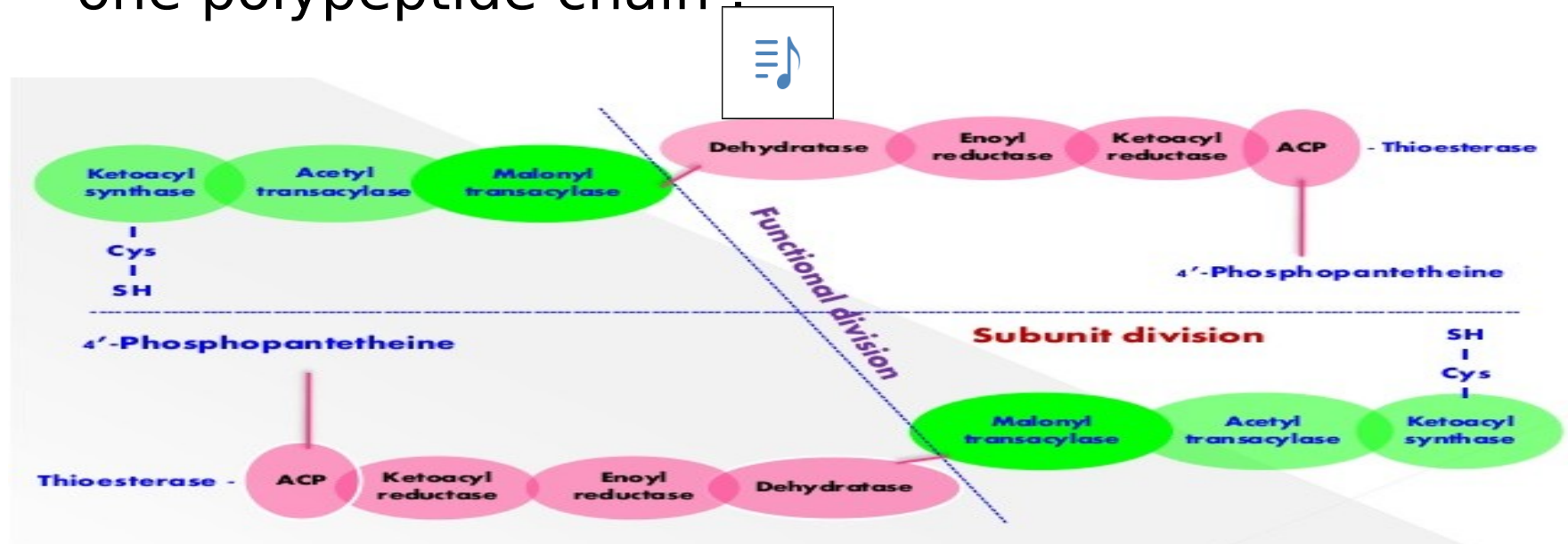


<http://diabesity.klebos.net/documents/fat.pdf>

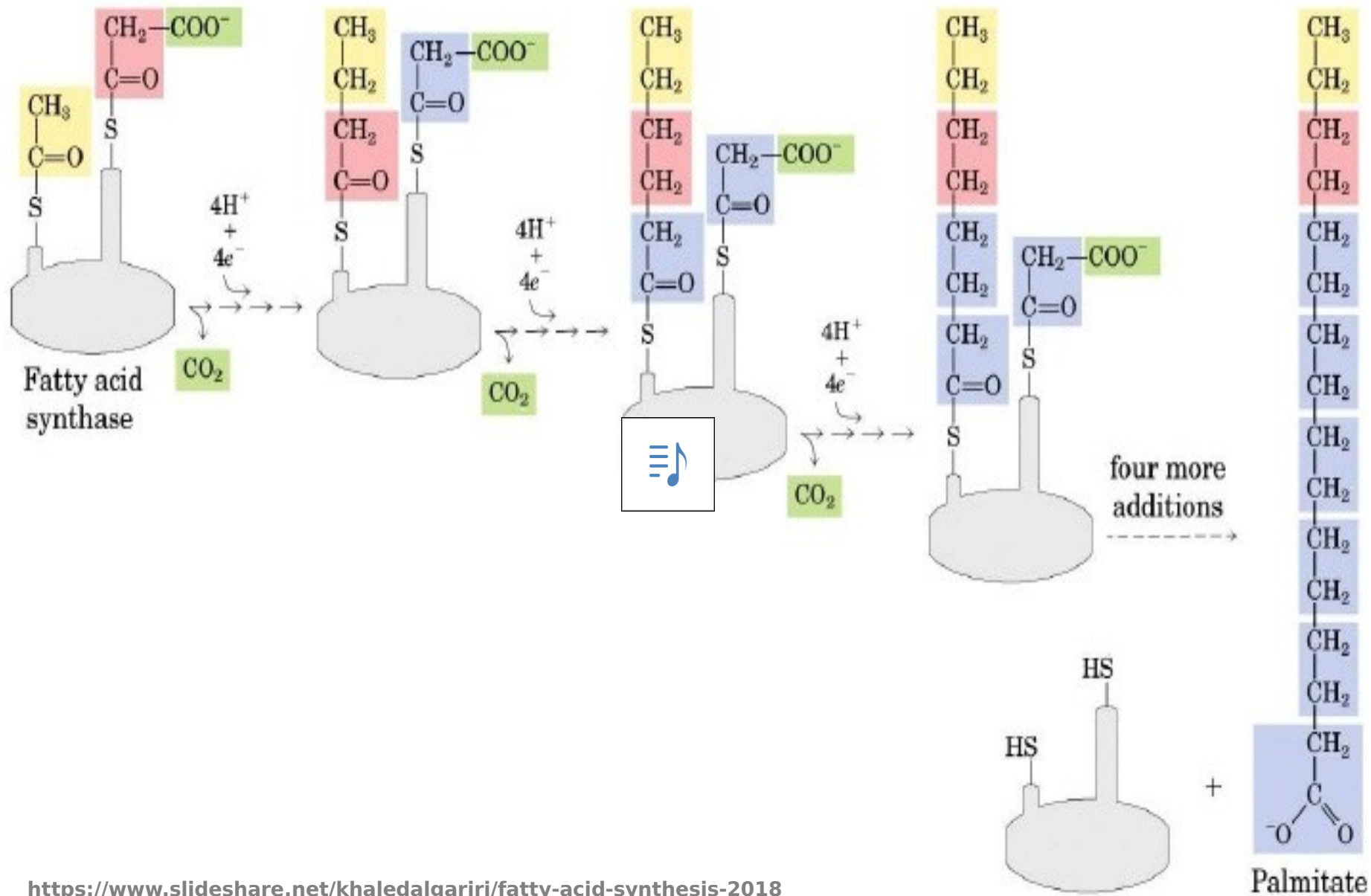
Steps of fatty acid synthesis

2. Fatty acid synthase (FAS)

- It is a **multienzyme complex**. It is a dimer enzyme consisting of 2 identical subunits, each subunit (monomer) has 7 enzyme activities on one polypeptide chain.



<https://www.slideshare.net/YESANNA/biosynthesis-of-fatty-acids-43420558>



<https://www.slideshare.net/khaledalgariri/fatty-acid-synthesis-2018>

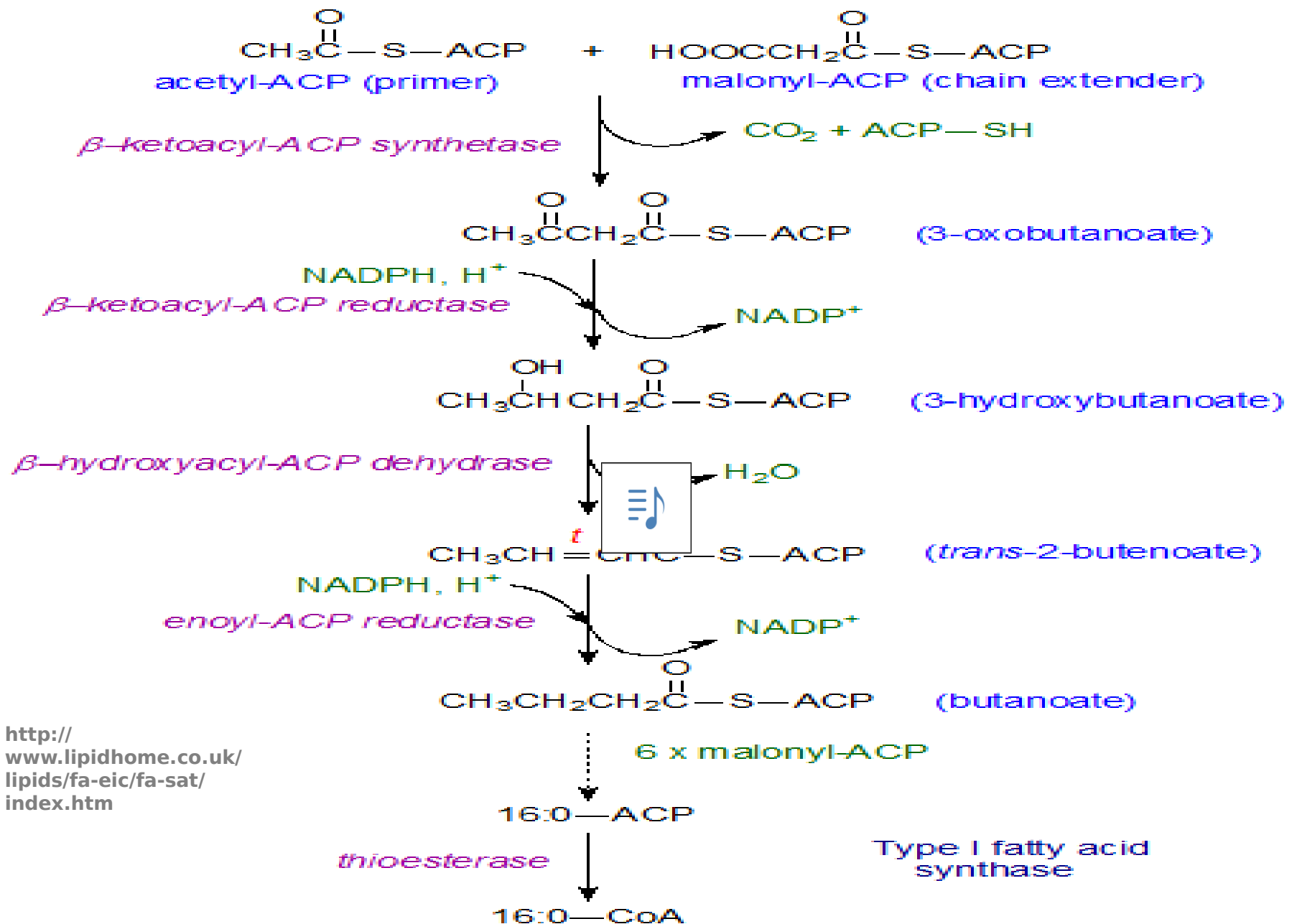
The fatty acid synthase enzyme catalyzed the following reactions :

- **Condensation step**
- **Reduction step NADPH**
- **Dehydration step**
- **Another reduction step NADPH**



The cycle is then repeated till the FA is synthesized.

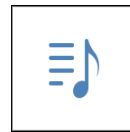




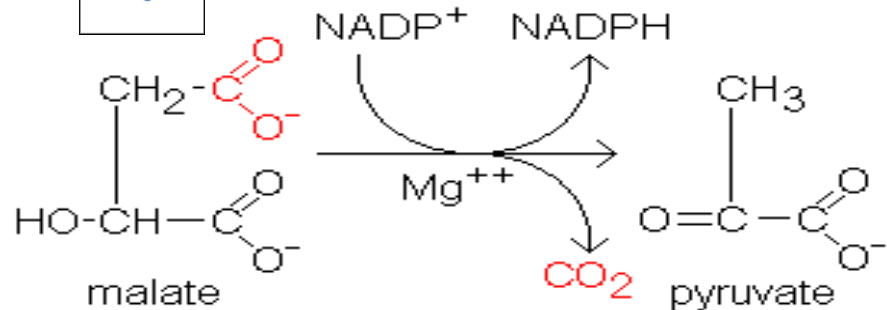
<http://www.lipidhome.co.uk/lipids/fa-eic/fa-sat/index.htm>

Sources of NADPH

1. HMP: G6P dehydrogenase
6-P gluconate dehydrogenase



2. Malic enzyme

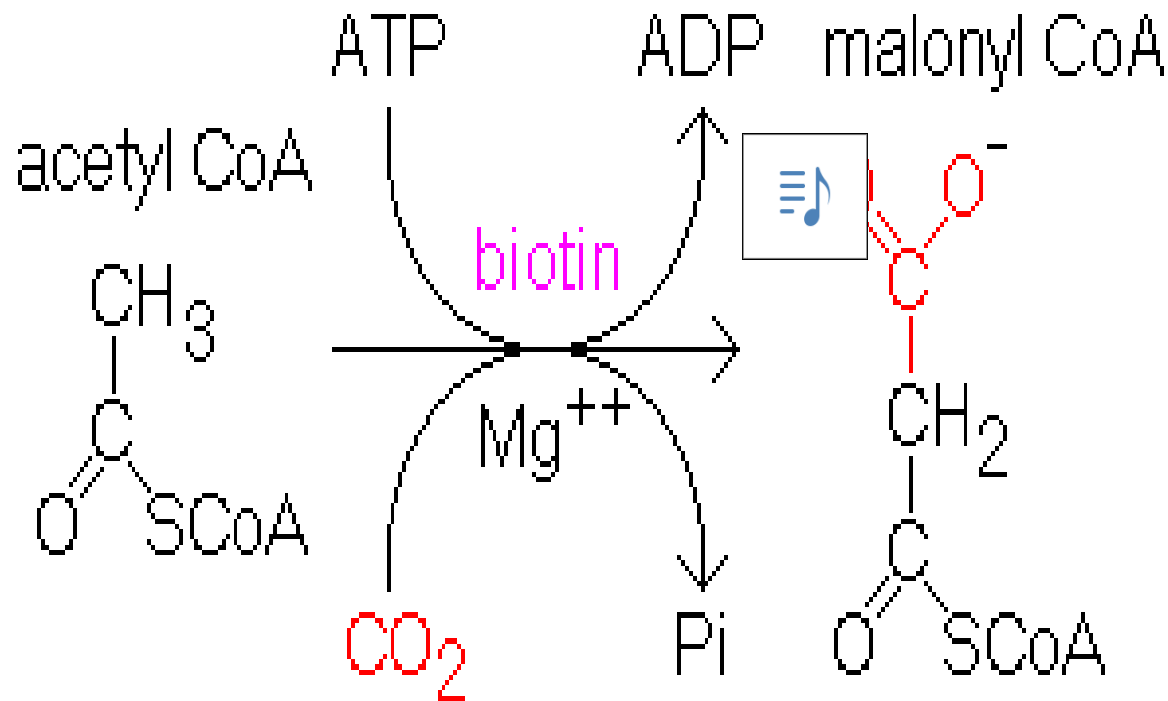


3. Cytosolic Isocitrate Dehydrogenase minimal role



Malonyl CoA is a key molecule during fatty acid synthesis. How can it be formed?

- By Carboxylation of Acetyl CoA by Acetyl CoA Carboxylase (ACC)



<http://www.bmb.leeds.ac.uk/illingworth/medics1/liver.htm>



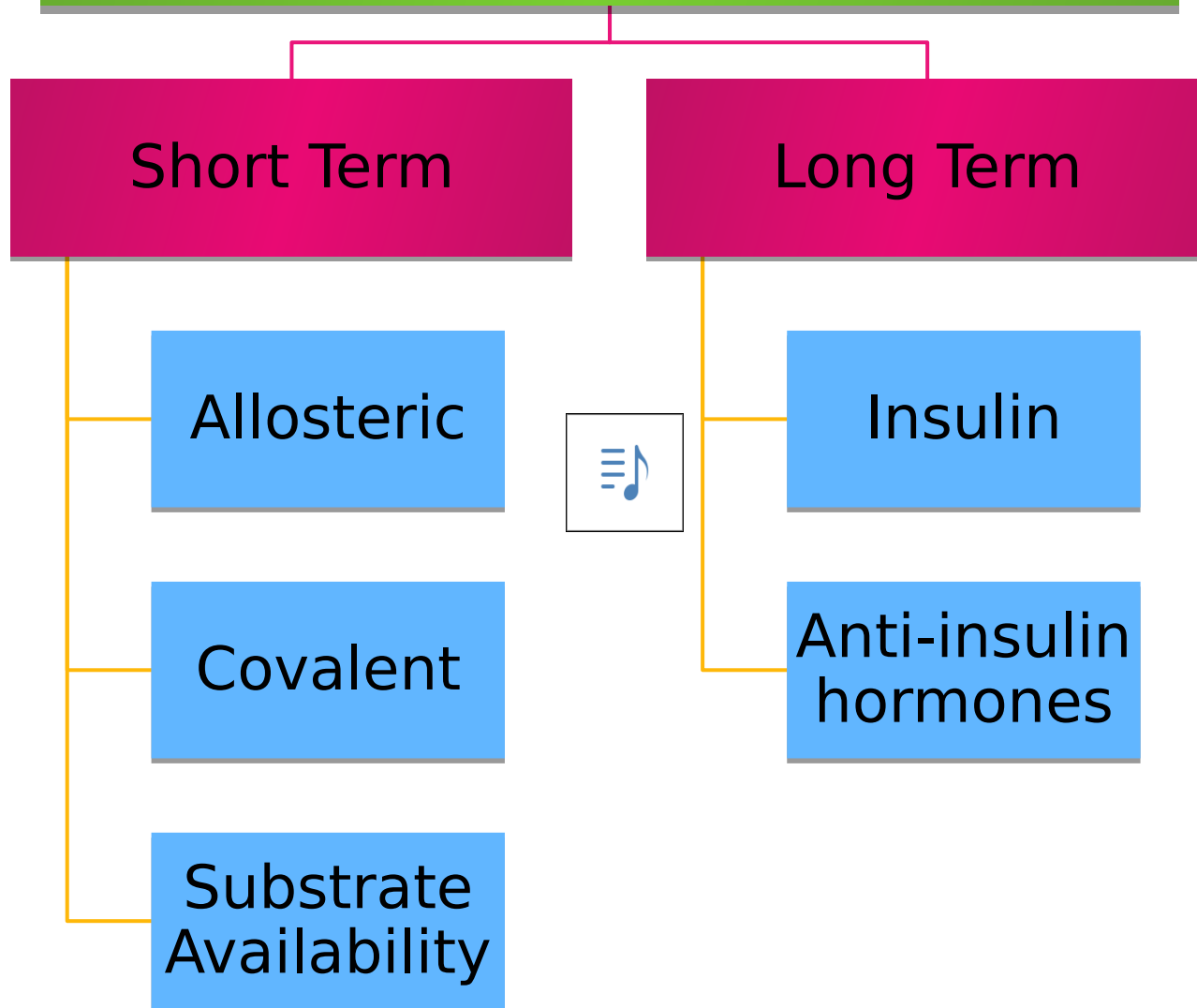
Regulation of FA Synthesis

Acetyl CoA Carboxylase (ACC)
(The committed/ The rate limiting step)



<https://giphy.com/gifs/adhd-P0m7wsn0F6MBG>

Regulation on ACC



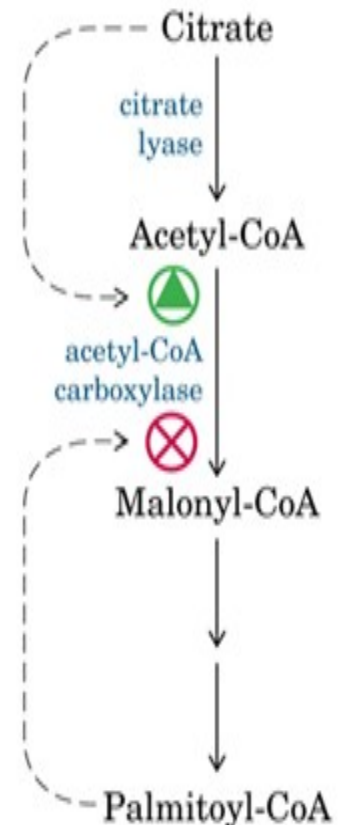
Allosteric Regulation of ACC

► Citrate

1. ↑ activity of ACC
2. Shuttles Acetyl CO~A to Cytoplasm

► Palmitoyl CO~A(product)

↓ activity of ACC (Feed back inhibition)



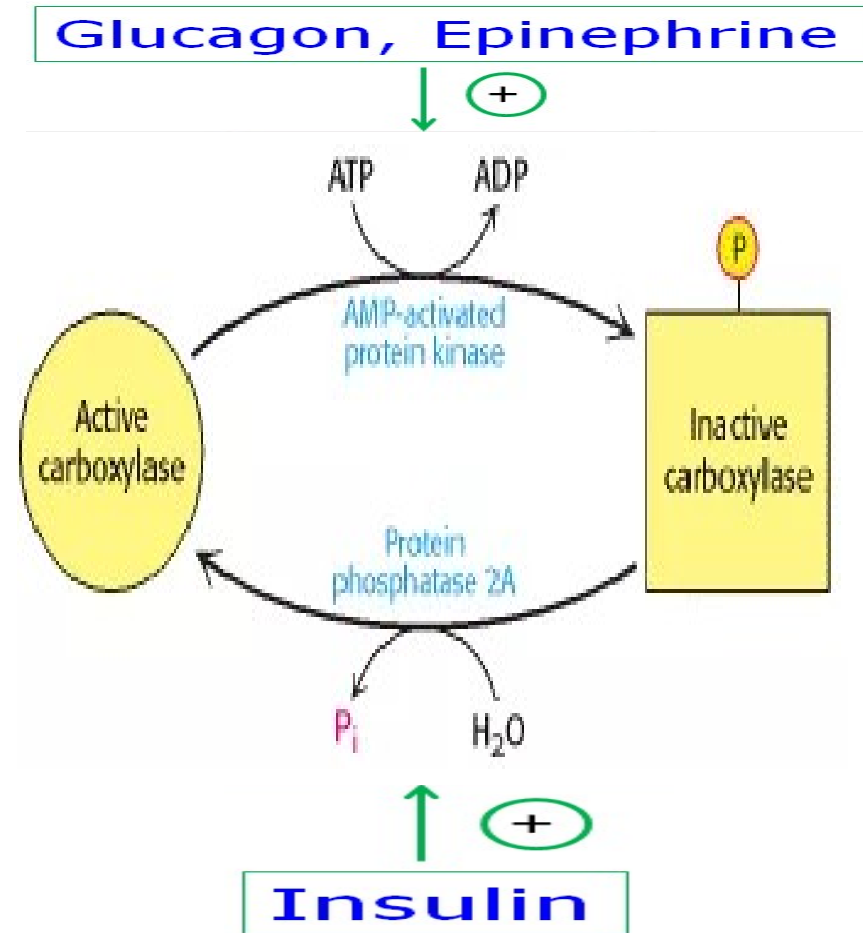
<https://www.namrata.co/regulation-of-fatty-acid-synthesis-a-quick-revision/>

Covalent Regulation of ACC

► Insulin:

↑ activity of ACC by
Dephosphorylation

► Glucagon & Epinephrine
↓ activity of ACC by
Phosphorylation through
the action of AMP-
activated protein kinase
(AMPK)



<https://slideplayer.com/slide/5012045/>

Substrate availability (its effect on ACC)

- **Increased CHO in diet → ↑ Insulin**

Glycolysis & PDH → Acetyl CoA

HMP pathway → NADPH

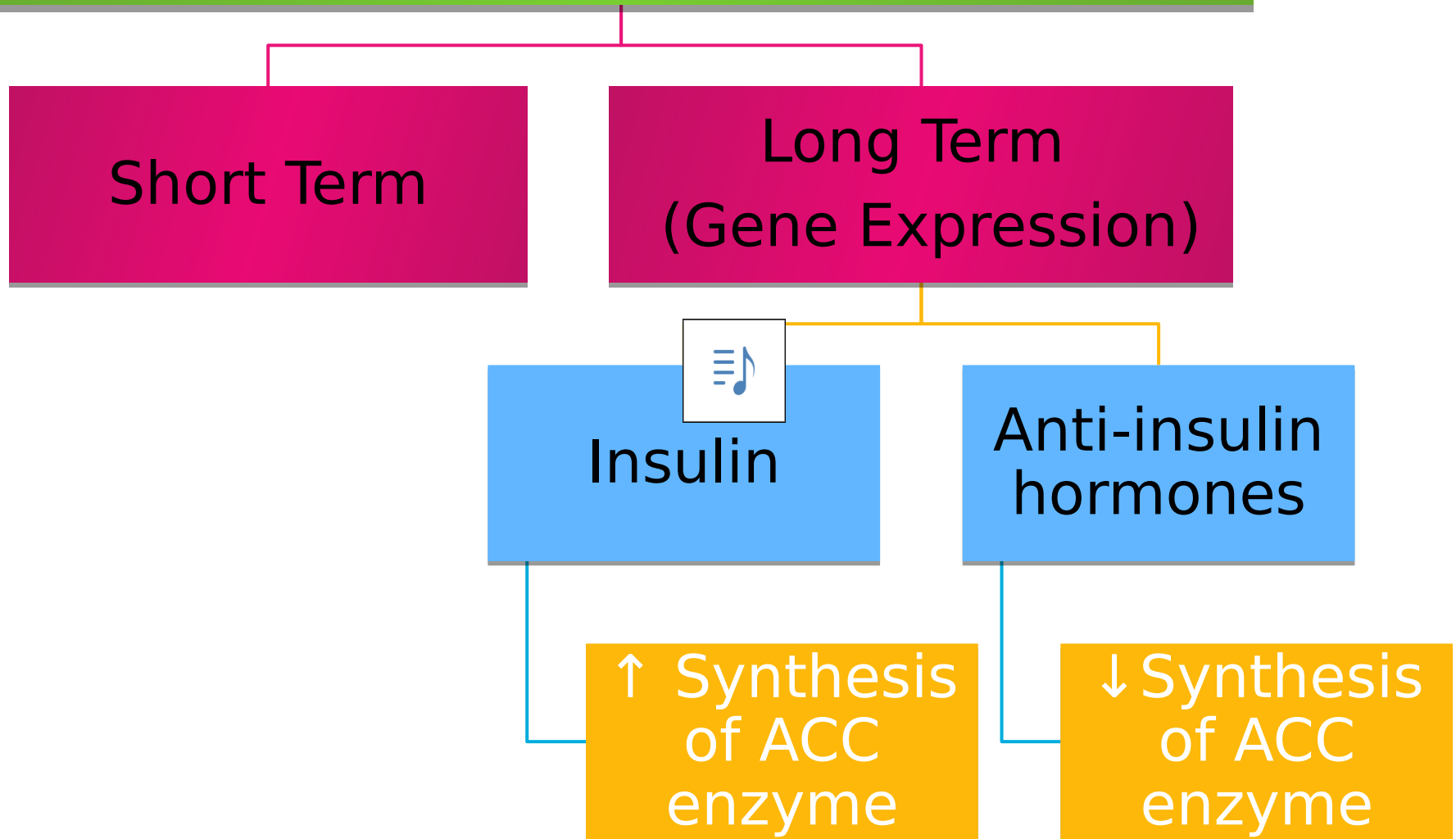


ACC, FAS expression



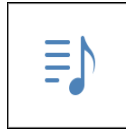
<https://metro.co.uk/2018/03/06/acknowledge-emotional-side-eating-well-never-combat-obesity-7365313/>

Regulation on ACC



The rate limiting enzyme in fatty acid synthesis is:

1. Propionyl CoA carboxylase,
2. Acetyl CoA carboxylase
3. Methylcrotonyl CoA carboxylase
4. Pyruvate carboxylase



Synthesis of Fatty Acids

There are two systems for fatty acid synthesis

I- Cytosolic de novo fatty acid synthesis

II- Microsomal system for fatty acid desaturation & elongation



II- Microsomal System for Fatty Acid Elongation

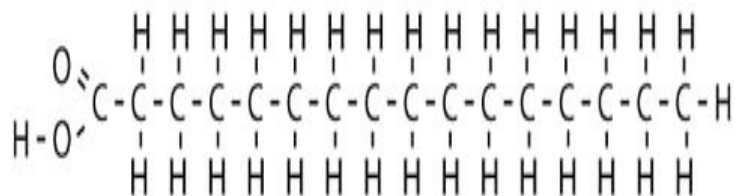
E.R. is the Major [most active] system for elongation of FA using:

Malonyl CoA as two-carbon units and

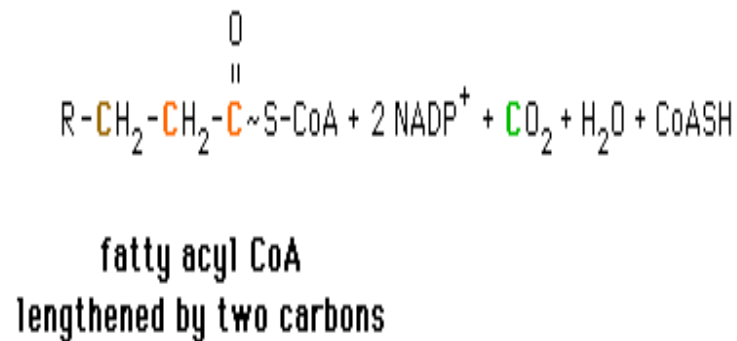
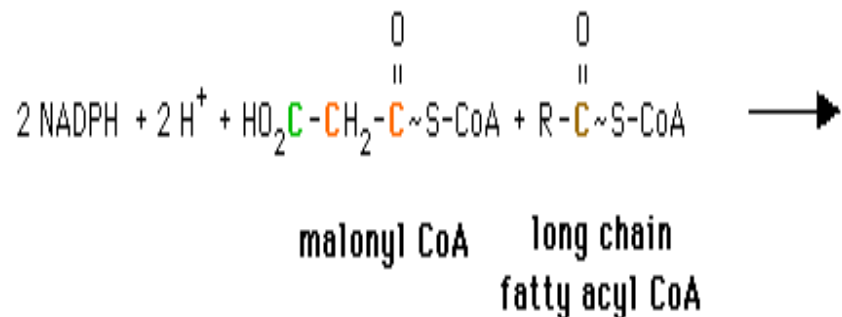
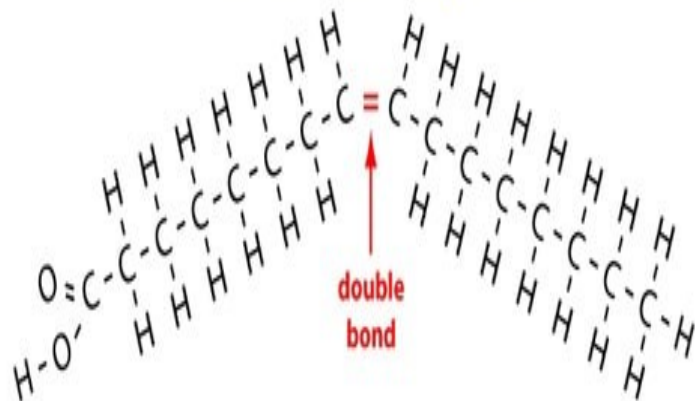
NADPH as hydrogen donor or

The brain has more elongation capabilities, to produce very-LCFA (22 C & 24 C) used for synthesis of brain lipids (during myelination).

saturated fatty acid



unsaturated fatty acid



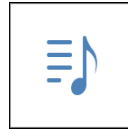
<http://www.perfectscorer.com/2017/10/chemistry-what-does-word-saturated-mean.html>

https://library.med.utah.edu/NetBiochem/FattyAcids/6_2a.html



A tissue with the most numerous fatty acid elongation capabilities:

- a. RBCs
- b. liver
- c. Cornea
- d. Muscles
- e. Brain



Key Points

- ▶ Citrate Shuttle plays a key role in Fatty acid synthesis.
- ▶ Synthesis of palmitic acid requires two sequential steps. 
- ▶ ACC can be regulated with different mechanisms.
- ▶ Palmitic acid can be elongated or desaturated to meet the cell's needs.



References

- ❑ **"Lippincott's Illustrated Reviews in Biochemistry" by P.C.Champe, R.A.Harvey and D.R.Ferrier**
- ❑ **"Harper's Biochemistry" by R.K.Murray, D.K.Granner, P.A. Mayes and V.W.Rodwell.**
- ❑ **Fundamentals of Clinical Chemistry (Tietz) Sixth**
- ❑ **"Textbook of Biochemistry with Clinical Correlations" by T.M.Devlin**
- ❑ ***www.namrata.co-* *Biochemistry for medics***



